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Commentary

The evolution of "pillars of therapy" to reduce heart failure risk and slow diabetic kidney disease progression

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ABSTRACT

The evolution of therapy to slow chronic kidney disease progression has changed dramatically over the last five years and is anticipated to change even more in the coming two to four years. What was traditionally noted as "renal sparing therapy" with blockers of the renin-angiotensin system (RAS) has now expanded to the use of inhibitors of sodium-glucose transport 2 (SGLT2) agents as well as the nonsteroidal mineralocorticoid receptor blocker, finerenone. These three "pillars of therapy" have slowed kidney disease progression by more than 50% compared to RAS blockers alone. Additionally, finerenone and SGLT2 inhibitors significantly reduce heart failure hospitalizations and the development of heart failure. Moreover, they improve exercise tolerance and reduce the risk of cardiovascular death, even though they do not affect atherosclerotic heart disease development. These data, taken together, demonstrate a "three pillar" therapy approach for cardiorenal risk reduction in people with type 2 diabetes who have any level of kidney disease.

The evolution of diabetic kidney disease (DKD) treatment has evolved over the past 50 years from essentially no therapy other than glycemic control to slow kidney disease in the late 1970s to now three distinctly different classes of drugs with a strong evidence base and level A recommendations in the guidelines (American Diabetes Association Professional Practice C et al., 2022) [1]. The added benefit of these agents to both glycemic and blood pressure control is that they not only slow DKD progression but also significantly reduce heart failure mortality and hospital admissions (American Diabetes Association Professional Practice C et al., 2022) [1].

These three drug classes include maximally dosed renin-angiotensin system (RAS) blockers, sodium-glucose co-transporter 2 (SGLT2) inhibitors, and the non-steroidal mineralocorticoid receptor antagonist (NS-MRA) inhibitor, finerenone. These agents provide additive cardiorenal risk reduction when used in concert compared to the submaximally dosed RAS blockers typically used as background therapy. Although the maximally tolerated dosages have been proven efficacious in outcome trials, the background therapy in most studies does not focus on maximally dosed RAS blockade. Hence, lower doses that fail to reduce risk are used [2].

Adding SGLT2 inhibitors and the NS-MRA, finerenone, to the traditional RAS inhibitor approach is reminiscent of how therapy evolved to treat heart failure with reduced ejection fraction. This started with low-dose beta-blockers, then the addition of RAS blockade followed by spironolactone and, more recently, the angiotensin receptor/neprilysin inhibitors (ARNIs) and SGLT2 inhibitors. All these drug classes independently showed that when added to the standard of care, further mortality and morbidity benefit occurred [3]. However, the benefits of these agents on slowing kidney disease progression were either not evaluated or absent in the early days of heart failure treatment. Data from post hoc analyses of more recent outcome trials demonstrate the preservation of kidney function and reduced incidence of new heart failure and heart failure hospitalization [4–7].

This paper will provide a perspective and focus on the NS-MRAs as the third pillar of therapy since there have been many papers and trials with SGLT2 inhibitors; however, these studies will be briefly discussed for context.

1. Sodium-glucose transport 2 (SGLT2) inhibitors

Perhaps the most recent and most extensive analysis of SGLT2 inhibitors on cardiovascular and renal outcomes in people with diabetes comes from a recent meta-analysis by McGuire and colleagues [6]. In this meta-analysis, the investigators document a significant risk

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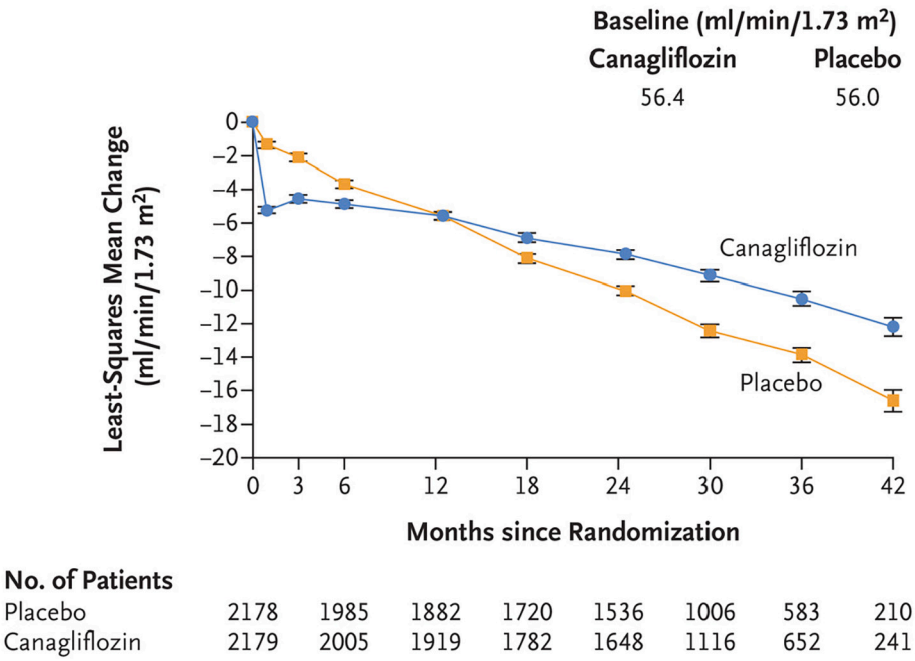

Fig. 1. Effects on albuminuria and estimated GFR. Panel B shows the change from the screening level in the estimated GFR in the on-treatment population. The | bars indicate the standard error in Panel B.

reduction in kidney disease progression and cardiovascular morbidity and mortality. More to the point, they show a decrease in dialysis initiation and heart failure hospitalizations and death [5].

All SGLT2 inhibitors were studied in patients already receiving RAS blockers. Thus, the outcomes benefit those already prescribed RAS blockers. From a kidney perspective, they reduced the risk of kidney disease progression by an additional 30 % over the already present approximately 20 % reduction in progression by the RAS blockers (Fig. 1).

SGLT2 inhibitors have multiple mechanisms of action that are beyond this article's scope. One such mechanism that is noteworthy is their effect on the microvasculature. A recent study investigated the connection between metabolic changes and cardiovascular function in the ob/ob−/− mice, a rodent model of early diabetes with a specific focus on coronary microvascular function. Due to a leptin deficiency, these mice develop metabolic syndrome/diabetes and hepatic steatosis. They also develop cardiac contractile and microvascular dysfunction, thus, a good model for translational studies of cardiometabolic diseases. The study tested the hypothesis that an SGLT2 inhibitor could directly affect the coronary microvascular function and contractile performance. The authors found that the SGLT2 inhibitor treatment of this mouse model mimics significant clinical findings regarding metabolism and cardiovascular improvements. Also demonstrated was that SGLT2 inhibition improves coronary microvascular function and contractile performance [8]. These measures are important because they have strong predictive values in humans for CV outcomes.

Note that SGLT2 inhibitors, however, do not reduce atherosclerotic disease events. The reader is referred to some excellent reviews on the topic for further exploration [9–11]. Suffice it to say; that this pharmacologic class should be thought of as “cardiorenal risk-reducing agents whose effects are not dependent on glucose lowering” [12].

The notion that SGLT2 inhibitors are diuretics is misleading since their diuretic effect disappears around an estimated glomerular filtration rate (eGFR) of 45 ml/min/1.73 m^2 when they lose the ability to lower serum glucose via increased urinary excretion. However, they continue to protect renal function down to the eGFR of 20 ml/min/1.73 m^2 [13].

An interesting side note is that this class's mechanism for lowering blood pressure has less to do with their natriuretic effect and more with their impact on the sympathetic nervous system. They mimic renal denervation as shown by Herat et al. in an animal model of chemical denervation versus dapagliflozin. The investigators demonstrated similar blood pressure reductions and neurohumoral effects, including depletion of tyrosine hydroxylase, the enzyme needed to generate norepinephrine, by both dapagliflozin and the active treatment group [11].

2. NS-MRA (finerenone)

In the heart, kidney, and blood vessels, mineralocorticoid receptor (MR) activation leads to pathological effects, such as excessive extracellular matrix accumulation, oxidative stress, and sustained inflammation. In these organs, the MR is expressed in cardiomyocytes, fibroblasts, endothelial cells, smooth muscle cells, and inflammatory cells. Thus, MR antagonism positively impacts a battery of cardiac and vascular pathological states, including heart failure, myocardial infarction, arrhythmic diseases, atherosclerosis, vascular stiffness, chronic kidney disease, and cardiac and vascular injury linked to metabolic comorbidities [14,15]. The novel pharmacologic class of nonsteroidal MR antagonists is distinctly different from steroidal agents and offers an improved safety profile while retaining their cardiovascular and renoprotective effects [14,16].

Finerenone is the only NS-MRA that has cardiorenal outcome data. This drug also affects both the kidney and the heart microcirculation. Studies in animal models with albuminuria evidence this. In Munich Wistar Fromter (MWF) rats, a model of chronic kidney disease related to alterations in extracellular matrix increased oxidative stress and endothelial dysfunction, finerenone demonstrated improvement in endothelial dysfunction through enhancing nitric oxide (NO) bioavailability and decreasing superoxide anion levels [17]. This benefit was due to an upregulation in vascular and renal superoxide dismutase activity. Additional studies demonstrated reduced arterial stiffness of mesenteric vessels, increased NO bioavailability, and clinical reduction in albuminuria.

While outcome trials with finerenone in heart failure are ongoing with the FINE ARTS trial, a minor proof of concept study for finerenone

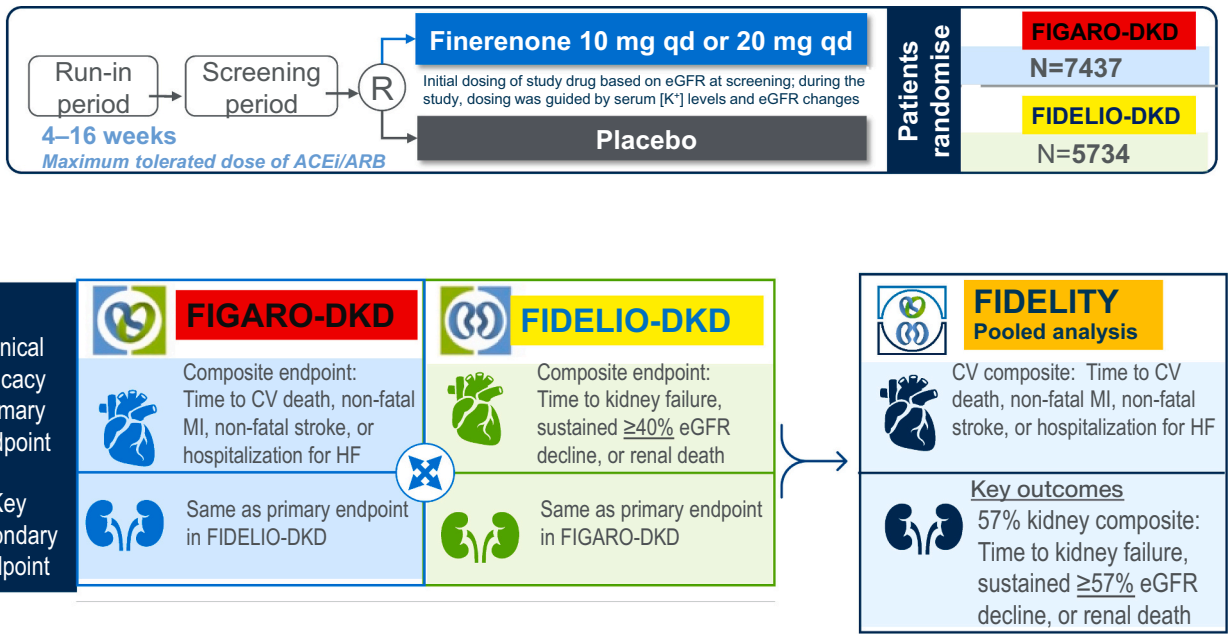

Fig. 2. Script.
The FIDELIO-DKD and FIGARO-DKD Phase III trials formed the largest cardiorenal outcomes program in CKD in T2D to date, investigating the efficacy and safety of finerenone, in over 13,000 patients on kidney and cardiovascular outcomes in patients with mild-to-severe CKD.[1,2]
Of these, 5734 patients in FIDELIO-DKD[1] and 7437 patients in FIGARO-DKD[2] were randomized to finerenone at 10 mg/day or 20 mg/day or to placebo.[1,2]
Both studies included a run-in period of 4 to 16 weeks, during which time cardiovascular and diabetes therapy was optimized, including RAS inhibitors which were titrated to a maximum tolerated labelled dose.[1,2]
The primary cardiovascular composite outcome in FIGARO-DKD of time to first onset of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure in FIGARO-DKD was the key secondary CV composite outcome in FIDELIO-DKD.[1,2]
Likewise, the primary kidney composite outcome in FIDELIO-DKD of kidney failure, sustained decrease in eGFR from baseline of more than or equal to 40 %, or renal death, was the key secondary kidney composite endpoint in FIGARO-DKD.[1,2]
The purpose of the FIDELITY analysis was to provide more robust estimates of safety and efficacy of finerenone compared with placebo.[3]
References: 1. Ruilope LM, et al. Am J Nephrol 2019;50:345–356; 2. Bakris GL, et al. Am J Nephrol 2019;50:333–344; 3. Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, et al. and Bakris GL. Eur Heart J. 2022;43(6): 474-84.

in addition to RAS blockers in patients with heart failure was performed. In an early cardiovascular study, finerenone was compared to eplerenone in a randomized, double-blind, phase 2b multicenter study, the MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF) of 1066 patients [18,19]. The study's primary endpoint was the percentage of individuals with a decrease of >30 % in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) from baseline to day 90. A key exploratory endpoint was the composite of death from any cause, cardiovascular hospitalizations, or emergency presentation for worsening HF until day 90. There was no difference in the percentage of patients who achieved an NT-proBNP decrease of >30 % from baseline to 90 days (37.2 % in the eplerenone group vs. 30.9–38.8 % in the finerenone groups). The composite clinical endpoint occurred less frequently in patients receiving finerenone daily compared to eplerenone. Still, this difference did not reach statistical significance except in the group who were initiated on 10 mg daily of finerenone titrated up to 20 mg daily (hazard ratio 0.56, 95 % confidence interval 0.35–0.90, p = 0.02) [19].

More recently, two double-blind, placebo-controlled outcome trials with finerenone, FIDELIO, and FIGARO provided great insight into its impact on cardiorenal outcomes. These trials were unique in that they used the same study design with different inclusion criteria and different primary endpoints (Fig. 2). Moreover, they were performed at recruitment sites worldwide but in the same countries. These trials were also designed to allow for a prespecified pooled analysis of all participants with distinct cardiorenal endpoints to capture the full impact of both problems. This was the FIDELITY analysis, the largest pooled (N = 13,124) analysis of patients with DKD studied by a unified protocol [20]. Both trials showed benefits in cardiovascular outcomes driven primarily by a decrease in heart failure hospitalizations. Slowing of DKD progression was also observed in both trials [21,22].

The results of these trials posed several questions. One dealt with the relative benefit of finerenone versus canagliflozin on renal and cardiovascular outcomes since they were each added to the background therapy of a RAS blocker. This analysis was subsequently performed and demonstrated similar risk reduction for heart failure and time to dialysis [23]. One exception, however, between these studies was that the finerenone trials included RAS blockers at maximally tolerated doses. Thus, a new question emerges: Does the combination of an SGLT2 inhibitor with finerenone provide a more significant cardiorenal risk reduction? While this can't be answered based on the current clinical trial data, there is an animal study that supports the benefit of the combination [24]. This study, performed in two different hypertensive rat models, demonstrated significant additive benefit in protection against cardiorenal fibrosis and reduced albuminuria when employing the combination versus either agent alone [24].

In addition, the combination of SGLT2 inhibitors and finerenone has shown a trend in further hyperkalemia risk reduction. This was noted in a post hoc analysis of the FIDELIO trial, demonstrating a lower risk of hyperkalemia among those on both finerenone and an SGLT2 inhibitor (p = 0.0023) [25]. Also, a trend toward a more significant reduction in albuminuria was seen by the combination in the FIDELITY analysis field [20]. An ongoing study, CONFIDENCE, evaluates the combination of an SGLT2 inhibitor and finerenone on albuminuria reduction in a randomized prospective study. Still, it is not powered for cardiorenal outcomes [26].

These data support the concept of a “pillared approach” to therapy in persons with diabetes and any level of kidney dysfunction (Fig. 3). This

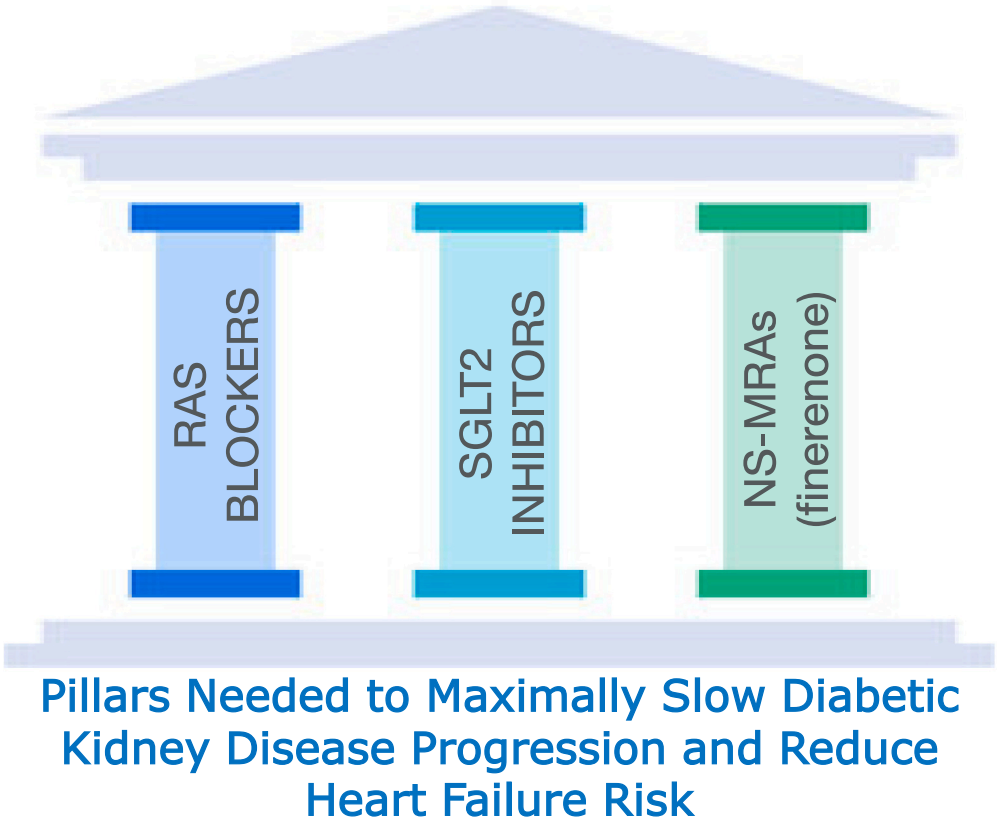

Fig. 3. Drug classes when used in combinations have been shown to slow kidney disease progression and reduce heart failure hospitalizations

novel approach for nephrologists would mirror what is now well established in the heart failure community. In short, maximally tolerated doses of a RAS blocker with an SGLT2 inhibitor and finerenone should provide maximal benefit to slow DKD progression and reduce heart failure hospitalizations.

3. How to effectively use an SGLT2 inhibitor with finerenone

It must be understood that these two agents need to be added to a maximally tolerated dose of a RAS blocker. Additionally, they should not be initiated simultaneously as both classes have variable acute hemodynamic effects, and the presence of a RAS blocker or diuretic may cause a significant drop in eGFR acutely of as much as 10–20 % [27]. Notably, up to a 25 % reduction in eGFR has been associated with better renal outcomes than no change in advanced kidney disease [27,28]. Moreover, recent data demonstrate that stopping blockers of the RAS system for increases in serum potassium also leads to poor renal outcomes [29].

While there are no prospective clinical trial data to support this approach, what has been done in both practice and the finerenone trials is summarized as follows: each drug should be used for at least a week to allow for equilibration of kidney function before the other is added. All patients need to be interrogated about volume status and encouraged to drink at least 1.5–2 l of fluid a day before use of these agents. Volume depletion will contribute to a rise in serum creatinine and is a common cause of the discontinuation of most drugs in most clinical settings [27,30].

One additional factor that will help guard against an excessive fall in eGFR is holding the diuretic for one week before starting these agents and restarting if needed a week after new drug initiation. Similar to the agents used in heart failure, the most pressing issue for each patient is whether improvement of glycemic control or blood pressure lowering is needed and should determine which agent to use first. If neither is pressing, the order doesn't matter as long as both are used. Remember, the "pillars of therapy" are needed for all three classes to reduce kidney disease progression and heart failure hospitalizations.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Blazek has no competing interest
Dr. Bakris has the following interests
Supported by T32 NIH grant DK07011 and is a consultant to Bayer, KBP Biosciences, Ionis, Alnylam, Astra Zeneca, Quantum Genomics, Novo Nordisk, Dia Medica Therapeutics, InREGEN Editor, Am J Nephrology.

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